REMARKS/ARGUMENTS

Reconsideration of the above-identified application is respectfully requested.

Summary of the Invention

The present invention is based on the discovery that the treatment of a cancer is enhanced by using combinations of a telomere damaging agent, such as paclitaxel, with an agent that inhibits telomerase, thereby reducing telomerase activity that leads to resistance to paclitaxel treatment. Applicants discovered that other cytotoxic treatments, such as, for example, cisplatin, radiation, hyperthermia, and serum starvation, also induce telomerase activity. Applicants discovered that combining paclitaxel with a telomerase inhibitory agent, such as 3'-azido-deoxythymidine (AZT) or 2', 3'-didehydro-3'deoxythymidine (d4T), results in a synergistic improvement in effectiveness of paclitaxel for treating cancers. These discoveries have led to the present invention. Applicants have further discovered that the AZT doses required to enhance the antitumor activity of paclitaxel are about 20-fold lower than the AZT doses used in the prior art for the treatment of HIV infection. Similarly, the Applicants discovered that AZT concentrations needed to enhance the paclitaxel activity are at least several folds lower than the AZT concentrations shown in the prior art needed to produce 50% inhibition of telomerase activity. Applicants further defined the AZT and d4T concentrations and the AZT doses that produce the greatest synergy with paclitaxel, whereas the prior art does not provide such enabling steps.

Claim Amendments

Claim 1 has been amended to claim the telomere damage-inducing agents paclitaxel and docetaxel, and a dosage of the telomerase inhibitory agents AZT and d4T, along with an enhancement of activity over either drug alone. There is support in the application for said dosages at p. 55 l. 15 – p.56 l.27 and for enhancement of activity throughout the specification and particularly at p. 14 ll. 1-6.

Claim 23 has been amended at the suggestion of the Examiner to remove the indefinite term "derivative." Claim 24 has been amended to continue to claim one telomerase inhibitory agent, AZT, and claim 26 refers to administration of a daily dose of AZT on a weight basis. Claim 27 has been amended as being dependent of claim 1 rather than claim 24, to relate to telomerase inhibitory agent d4T, and to more particularly point out the matter claimed.

Claim 28 and 126 has been amended to correct an informality due to a typographical error, and to particularly point out what the applicants consider a subtherapeutic dose. There is support in the application for said doses in the specification at p. 26 ll. 8-16. See also the declaration of Dr. Au of September 8, 2004, submitted herewith.

Claims 33-35 have been withdrawn from prosecution as being drawn to non-elected species.

Claim 42 has been amended to claim only the telomere-damage inducing agents paclitaxel and docetaxel, the telomerase inhibitory agents AZT and d4T, and to specifically point out the enhancement of the combination drug therapy over that of either drug alone. Where claim 1 is drawn to a method for inhibiting or reducing the growth of a cell, claim 42 is directed to a method of treating cancer. Claims 44-47 have been amended to conform with the amendments to claim 42. The dependency of claims 90 and 91 have been changed to depend on claim 42, and the dose ratios previously present in claim 91 have been replaced with actual doses based on the ratios. There is support in the specification throughout Example 8. See also the declaration of Dr. Au of September 8, 2004.

Claims 93 –96 and 99-101 have been withdrawn from prosecution as being drawn to non-elected species.

Claim 97 has been amended to claim telomerase inhibitory agents identified in the application at p.20, Table 1, and to claim a synergistic effect. There is support in the application for a synergistic effect. The synergistic nature of the combined drug effects of the telomere damage-inducing agent and the telomerase inhibitory agent has support in the application at p. 57, l. 5 – p. 58 l. 12 and is claimed so as to clearly show as major feature of Applicants' invention.

Claim 126 has been amended to particularly point out what the applicants consider a subtherapeutic dose. There is support in the application for said doses in the specification at p. 26 ll. 8-16. See also the declaration of Dr. Au of September 8, 2004.

New claims 127 and 128 were added to claim previously disclosed matter for non-human animals, which finds support throughout the specification in the Examples and in particular at p. 12, ll. 18-20.

No admission regarding patentability should be presumed or inferred from these amendments and cancellations.

Claim Rejections

Claim Rejections 35 USC §112, first paragraph.

Claims 1, 3-24, 28, and 42-45, 93, 97-98 102-123 stand rejected under 35 U.S.C. 112, first paragraph, as not reasonably providing enablement for inhibiting or reducing the growth of a cell or for treating cancer using a combination of paclitaxel and a nucleoside or nucleotide analog other than AZT or d4T. Although Applicants respectfully disagree that undue experimentation is required to identify telomere damage-inducing agents and telomerase inhibitory agents in light of the Declaration of Dr. Au filed December 29, 2003, in order to advance prosecution of the application to allowance, Applicants have amended the claims to claim only those telomere damage-inducing agents and telomerase inhibitory agents with efficacy demonstrated in the application. Claim 97 has been amended to claim those compounds for which telomere damage-inducing activity or telomerase inhibitory activity is known. The Declaration of Dr. Au of September 8, 2004 states her opinion as a skilled artisan that the agents claimed in claim 97 are very likely to similarly display the efficacy taught in the application. Thus, Applicants have overcome this objection.

Claim Rejections 35 USC §112, second paragraph.

Claims 23-24, 28, 44-45, 90-91, 122-123, and 126 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Applicants have amended the claims at the Examiner's suggestion, and removed the term "derivative" from all claims. Applicants set forth in claim 28 the bounds of a subtherapeutic dose for paclitaxel and docetaxel. Claims 27 and 90 have been amended to claim tissue concentrations of about 20 micromolar. Such tissue concentrations are readily determined and titrated without undue experimentation by practitioners. See Declaration of Dr. Au dated September 8, 2004.

Although the specification discloses a formula for determining relative drug concentrations by which to achieve specific dose ratios, in order to advance prosecution, Applicants have amended claims 1 and 91 to point out specific subtherapeutic doses of AZT and d4T not present in the art that represent the ratios previously claimed.

By these claim amendments, Applicants have overcome the Examiner's rejection based on 35 U.S.C. §112, second paragraph, and Applicants respectfully request that this rejection be withdrawn.

Claim Rejections 35 U.S.C. §102(b), based on Gill.

Claims 1, 3-4, 8-10, 12-14, 16, 18, 20, 22-24, 26, 42-46, 97-98, 102-103,107-109, 111-113, 115, 117, 119, and 121-123 stand rejected under 35 U.S.C. §102(b) as being anticipated by Gill (US patent No. 5,756,537). Gill teaches that paclitaxel can be administered concurrently with AZT for the treatment of Kaposi's Sarcoma in patients with acquired immunodeficiency syndrome (AIDS).

Applicants have amended independent claims 1, 42 and 97 to claim an enhanced effect upon combined treatment with a telomerase damage-inducing agent such as paclitaxel and a telomerase inhibiting agent such as AZT or d4T. It is clear from the application that combined treatment with these two classes of drugs leads to a greater than additive effect of the two drugs alone. Claim 1 has been amended to claim subtherapeutic doses of AZT and d4T that are less than the lowest doses indicated for treating retroviral infection and AIDS, the only treatments for which these drugs are currently indicated. See Declaration of Dr. Au, September 8, 2004. While Gill does disclose that paclitaxel can be used in AIDS patients who receive AZT, Gill does not teach that adding AZT, d4T, or other reverse transcriptase inhibitors, through inhibition of telomerase, enhances the antitumor activity of paclitaxel. Thus, this art use of paclitaxel does not enable an improved treatment of cancer, or inhibition of cellular growth. Hence, in the absence of the present invention, there is no motivation to use AZT, d4T or other reverse transcriptase inhibitors to enhance the telomere-directed effect of paclitaxel. In consideration that Applicants by amendment claim an effective dose less than is indicated by Gill, Applicants have overcome this objection.

Claim 42 specifically claims an enhanced effect of combination treatment with the telomere damage-inducing agent paclitaxel or docetaxel, and a telomerase inhibitory agents AZT or d4T, resulting in an enhancement of activity over either drug alone. Claim 97 claims other telomere damage-inducing agents and telomerase inhibitory agents disclosed in the application and claims a synergistic effect, as defined in the application. (See p. 13, ll. 27-33) The enhanced or synergistic nature of the combined drug effects of the telomere damage-inducing agent and the telomerase inhibitory agent has been recited in claims 1, 42, and 97 so as to clearly show the major feature of Applicant's invention. Gill shows no evidence of improved therapeutic response to the combination of AZT and paclitaxel, and in fact does not differentiate between Kaposi's sarcoma patients receiving AZT and those that are not. Thus, Gill is completely devoid of any evidence for an enhanced response to the combination of AZT and paclitaxel. It is simply impossible for any artisan to infer from Gill that the combination of AZT with paclitaxel will lead to improved treatment of patients not infected with HIV, let alone improved treatment for other

cancers. The Examiner has admitted that "Gill does not teach any synergistic benefit using the combination." Gill, nonetheless, offers no motivation at all for a practitioner to combine paclitaxel with AZT. Thus, Applicants' invention of the enhanced effect of a combination of a telomere damage-inducing agent, such as paclitaxel with a telomerase inhibitor, such as AZT or d4T is not anticipated by any prior art.

The law is clear that an unrecognized occurrence does not anticipate Applicants' invention. Gill does not recognize that combining a telomere damaging agent, such as paclitaxel, with a telemorase inhibitor, such as AZT or d4T, will lead to enhanced treatment effectiveness. The combination of paclitaxel with AZT is simply not inherent in the treatment practiced by Gill. "Inherency cannot be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances [such as combining paclitaxel with AZT] is not sufficient." Ex parte Skinner 2 USPQ 2d 1788, 1789 (BPAI, 1987). That a patient with AIDS may by coincidence receive both paclitaxel and AZT does not anticipate all combinations of AZT with paclitaxel for cancer treatment of any kind because there is no motivation to combine these drugs, and the combination is not inherent in cancer treatment. In light of Applicants' amendments to specifically point out the features of their invention, Applicants request that the Examiner's rejection in light of Gill be withdrawn.

Claim Rejections 35 U.S.C. §103, Based on Gill in view of Merck Index and Cheng

Claims 1, 3-4, 6-24, 26-28, 42-47, 90-91, 97-98, 102-103, 125-126 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Gill, in view of the Merck Index, and in view of Cheng *et al.*, (U.S. 5,869,461). Gill teaches that paclitaxel can be administered concurrently with AZT to treat Kaposi sarcoma in AIDS patients, and that paclitaxel can be used with other antiretroviral agents that are used to treat AIDS. The Merck Index teaches that d4T is a reverse transcriptase inhibitor. Cheng teaches that administration of AZT is generally 5 – 50 mg/kg/day.

Not only is it not obvious to combine paclitaxel and AZT for enhanced therapeutic effect in inhibiting cellular growth, it is contrary to medical indications for the treatment of HIV. A reduced dose of AZT could lead to the selection AZT resistant virus, and potentially mortality. Cheng actually provides support for the Applicants argument that there is a minimum indicated dose of AZT for HIV treatment, and that dose is higher than the dose effective for showing an enhanced effect under the Applicants' invention. As discussed above, Gill provides absolutely no motivation to combine drugs for an enhanced effect. Hence, Gill in combination with any other reference does not render claims 1, 3-4, 6-24, 26-28, 42-47, 90-93, 97-98, 102-103, 125-126 obvious.

Conclusion

In view of the amendments and remarks submitted herewith, allowance of the claims and passage to issue of this application respectfully are requested.

Respectfully submitted,

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